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10/501,957	07/21/2004	Samuel G. Steinemann	S0004/7003US0	8443

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EXAMINER	
HEYER, DENNIS	
ART UNIT	PAPER NUMBER
1628	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/501,957	STEINEMANN ET AL.	
	Examiner	Art Unit	
	DENNIS HEYER	1628	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 August 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-70* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgement is made of Applicant's remarks and amendments filed August 2, 2010. Acknowledgement is made of Applicant's amendment to Claims 28, 41, 51 and 70 in the response filed August 2, 2010. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Status of Claims

Claims 28 – 70 are currently pending.

Withdrawn Rejections

Claim rejections – 35 USC § 112 – 2nd Paragraph

The rejection of Claims 28, 51, 52 and 70 under 35 U.S.C. 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is rendered moot and is withdrawn in response to Applicant's amendments.

Maintained Rejections

Claim rejections – 35 USC § 112 – 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 41 *remains* rejected under 35 U.S.C. 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 41 recites the limitation "the implant of Claim 28, wherein the systemic hormone comprises one or more of 1, 25-$(OH)_2D_3$, 1α, 1-$(OH)_2D_3$ and 24, 25-$(OH)_2D_3$" There is insufficient antecedent basis for this limitation in the claim. Instant Claim 28, from which Claim 41 depends, requires that the systemic hormone be a polypeptide. The systemic hormones cited in instant Claim 41 are, in fact, non-peptide steroid-based vitamin D compounds. In view of the lack of clarity of the term systemic hormones (polypeptide and/or steroid hormone), for the purpose of examination on the merits, limitations drawn to solution concentrations and percent surface coated as disclosed in the prior art will be considered as reading on both polypeptides *and* systemic hormones.

Response to Arguments

Applicant has amended Claim 41 to recite the limitation "wherein the polypeptide comprises systemic hormones comprisesing one or more of 1,25-$(OH)_2D_3$, $l\alpha$,1,25$(OH)_2D_3$ and 24,25-$(OH)_2D_3$.

Applicant argues that "The term systemic hormones include several different classes of compounds. These classes are peptides, polypeptides, steroids and derivatives of amino acids, such as thyroxin (see enclosed printouts Benninghoff, Drenckhahn, Anatomie, Band 2, 6. Auflage, Verlag Elsevier, Urban & Fischer Verlag. 2004, page 186, left column, last paragraph (in German) and Sonia Ciarmatori, "The role of IGFIIGFBP system in the proliferation and differentiation of chondrocytes", summary). See also the present specification at page 10 paragraph 6 which lists the specific compounds of claim 41 as systemic hormones and includes literature citations" (Remarks, page 9, 3rd paragraph).

This argument is not found to be persuasive because there *remains* insufficient antecedent basis for this limitation in the amended claim. The Examiner agrees that systemic hormones include compounds from several different structural classes of compounds, including polypeptides and steroids. However, instant Claim 28, from which amended Claim 41 depends, still requires that the systemic hormone be a *polypeptide* ("wherein the polypeptide is selected from the group consisting of one or more transforming growth factors (TGF) and systemic hormones"), and, as noted in the previous Office Action (mailed February 2, 2010), the systemic hormones cited in instant Claim 41 are, in fact, non-peptide steroid-based vitamin D compounds. Thus in

spite of the alleged support in the specification for the steroid hormones recited in Claim 41, the implant of Claim 28, as written, is drawn exclusively to polypeptides.

Claim rejections – 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 28, 31, 33, 44, 48, 51, 52 and 70 *remain* rejected under 35 U.S.C. 102(b) as being anticipated by Cole *et al.* in Clinical Orthopaedics and Related Research, 345, 219 – 228 (1997) as evidenced by Schrier *et al.* in AAPS PharmSciTech 2001; 2(3) article 18 and Israel *et al.* in US 2008/0139474 (published June 12, 2008).

Cole *et al.* teach that the transforming growth factor, human bone morphogenic protein (BMP-2), enhances bone formation in rats by direct application to a titanium implant surface (Abstract, page 227, final paragraph; instant Claims 28, 31, 33). BMP-2 contains the amino acid tryptophan which has a heterocyclic ring (instant Claims 40 and 56) as evidence by Israel *et al.* (Figure 1, amino acid sequence of BMP-2). Cole teaches bringing a roughened cylindrical titanium implant into contact with a BMP-2 stock solution of 2300 µg/mL (~ 78 µmol/L) (page 220, Recombinant Human Bone Morphogenic Protein Section, an 'applying' step, as recited in amended Claim 51) which

is within the limitation of polypeptide concentrations recited in instant Claims 44 and 48. Note that the molar concentration of BMP-2 was calculated using a molecular weight of 32K Daltons as evidenced by Schrier *et al.* ("rhBMP-2 is a 32-kd homodimeric protein"; page 1, Introduction, 3rd paragraph).

Accordingly, although Cole does not explicitly teach the "rate" or, the percent of the titanium surface, coated with monomolecular layer of polypeptide, because Cole teaches bringing the same polypeptide (BMP-2) solution into contact with a roughened titanium implant at the same concentrations recited in instant Claims 44 and 48, the amount of the surface of the titanium implant coated will fall into the same ranges recited in instant Claims 28, 51, 52 and 70. "[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." Atlas Powder Co. v. Ireco Inc., 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. In re Best, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). >In In re Crish, 393 F.3d 1253, 1258, 73 USPQ2d 1364, 1368 (Fed. Cir. 2004), the court held that "just as the discovery of properties of a known material does not make it novel, the identification and characterization of a prior art material also does not make it novel." In the instant case the Applicant merely *characterizes* the percent surface coated by the polypeptide BMP-2 in the titanium implant of Cole (Claims 28, 51, 52 and 70).

Accordingly, absent a specific showing of evidence to the contrary, the composition of Cole has the same percent surface coated with a monomolecular layer of polypeptide.

Claim rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 28 – 31, 33, 40, 42 – 60 and 63 – 70 *remain* rejected under 35 U.S.C. 103(a) as being unpatentable over Steinemann *et al.* in WO00/44305; published: August 03, 2000, in view of Cole *et al.* in Clinical Orthopaedics and Related Research, 345, 219 – 228 (1997) as evidenced by Schrier *et al.* in AAPS PharmSciTech 2001; 2(3) article 18 and Israel et al. in US 2008/0139474 (published June 12, 2008).

It is noted that, for ease of examination, the Examiner relied upon US Patent 6,702,855 as an equivalent English translation of the German language application PCT/EP00/00619 (WO 2000/44305). US Patent 6,702,855 is a national stage entry of PCT/EP00/00619 (WO 2000/44305). All citations henceforth to Steinemann *et al.* are located in the US Patent.

Steinemann teaches an osteophilic implant with improved osteointegration properties. The implant is made of titanium metal whose surface is partially roughened and in the hydroxylated state (Abstract; instant Claims 28 and 29). The macro- and micro-roughness limitations on the titanium surface of the implant are taught by Steinemann on column 3, lines 52 – 59 and in Example 1 (column 7, lines 26 – 35; instant Claims 30 and 53 – 55).

Regarding packaging of the implant, Steinemann teaches the implant is packaged "preferably sealed in a gas-tight and liquid-tight covering" (column 5, lines 30 – 38) and that the implant assembly comprises a vessel having an inert atmosphere and a medium that is at least partially filled with water (column 5, lines 43 – 46, Claims 2 and 4 – 6; instant Claims 42 and 57 – 58). The limitation of packaging the implant in "pure water' is taught in Example 1, lines 40 – 41.

Steinemann teaches that suitable additives are incorporated into pure water including mono- and divalent cations and anions in amounts ranging from 50 to 250 meq/l (column 5, lines 57 – 67 and column 6, lines 1 – 14; instant Claims 45 – 46, 59 and 63 – 66).

Steinemann teaches a process for roughening the implant surface by initial sandblasting and a subsequent chemical etching process (column 7, Example 1, lines 26 – 35, Claims 37 – 39; instant Claims 67 – 69), with the resulting material being an implant, as well as a dental implant (column 7, lines 47 – 51, instant Claims 47 and 49 50). Further, Steinemann teaches a process for introducing a partially cylindrically shaped dental implant into the cavity of a jaw bone (column 7, lines 47 – 52, instant Claim 51).

Steinemann does not teach an osteogenic implant comprising polypeptides.

Cole *et al.* teach that the transforming growth factor, human bone morphogenic protein (BMP-2), enhances bone formation in rats by direct application to a titanium implant surface (Abstract, page 227, final paragraph; instant Claims 28 – 29, 31, 33, 47 and 51). BMP-2 contains the amino acid tryptophan which has a heterocyclic ring (instant Claims 40 and 56) as evidence by Israel *et al.* (Figure 1, amino acid sequence of BMP-2). Cole teaches bringing a roughened cylindrical titanium implant into contact with a BMP-2 stock solution of 2300 µg/mL (~ 78 µmol/L) (page 220, Recombinant Human Bone Morphogenic Protein Section; an 'applying' step, as recited in amended Claim 51) which is within the limitation of polypeptide concentrations recited in instant Claims 44 and 48. Note that the molar concentration of BMP-2 was calculated using a molecular weight of 32K Daltons as evidenced by Schrier *et al.* ("rhBMP-2 is a 32-kd homodimeric protein"; page 1, Introduction, 3rd paragraph).

Accordingly, although Cole does not explicitly teach the "rate" or, the percent of the titanium surface, coated with a monomolecular layer of polypeptide, because Cole

teaches bringing the same polypeptide (BMP-2) solution into contact with a roughened titanium implant at the same concentrations recited in instant Claims 44 and 48, the amount of the surface of the titanium implant coated will fall into the same ranges recited in instant Claims 28, 51, 52 and 70. "[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." Atlas Powder Co. v. Ireco Inc., 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. In re Best, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). >In In re Crish, 393 F.3d 1253, 1258, 73 USPQ2d 1364, 1368 (Fed. Cir. 2004), the court held that "just as the discovery of properties of a known material does not make it novel, the identification and characterization of a prior art material also does not make it novel." In the instant case the Applicant merely *characterizes* the percent surface coated by the polypeptide BMP-2 in the titanium implant of Cole (Claims 28, 51, 52 and 70). Accordingly, absent a specific showing of evidence to the contrary, the composition of Cole has the same percent surface coated with a monomolecular layer of the polypeptide.

It would have been *prima facie* obvious for one of ordinary skill in the art to cover the titanium surface of Steinemann with a bone morphogenic protein, such as BMP-2 to provide an osteogenic implant. One would have been motivated to do so, at the recited concentration ranges, with a reasonable expectation of success, because Cole teaches

that the combination of BMP-2 on a roughened titanium implant surface is osteogenic, i.e. enhances bone formation, in rats.

Claims 41 and 61 – 62 *remain* rejected under 35 U.S.C. 103(a) as being unpatentable over Steinemann *et al.* in WO00/44305; published: August 03, 2000, in view of Cole *et al.* in Clinical Orthopaedics and Related Research, 345, 219 – 228 (1997) as evidenced by Schrier *et al.* in AAPS PharmSciTech 2001; 2(3) article 18 and Israel et al. in US 2008/0139474 (published June 12, 2008), as applied to Claims 28 – 31, 33, 40, 42 – 60 and 63 – 70, and further in view of Lohmann *et al.* in Journal of Bone and Mineral Research, 15, 1169 – 1180 (2000).

Steinemann in combination with Cole teach an osteogenic implant, and preparation thereof, of a micro and macro roughened titanium surface and a polypeptide within the recited concentration and percent coating limitations.

The combination of Steinemann and Cole do not teach the systemic hormones as recited in instant Claim 41 nor the limitations of contacting the titanium metal surface with a peptide or systemic hormone solution a the lower ranges from 0.1 to 10 µmol/l or about 1 µmol/l (instant Claims 61 and 62). As noted above, Claim 41 has been rejected for lacking antecedent basis because the compounds recited are not peptides.

Lohmann teaches the response of osteogenic cells to surface roughness and 1,25-dihydroxyvitamin D_3 (1,25-$(OH)_2D_3$ (Title). Lohmann teaches osteogenic cell differentiation was enhanced on roughened titanium surfaces, and further enhanced by the addition of 1,25-$(OH)_2D_3$ at a concentration of 10^{-7} M (0.1 µmol/l; Abstract, instant Claims 40 and 61). This concentration is within the range recited in instant Claim 61.

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art, at the time the invention was made, to contact the titanium implant at the lower polypeptide or hormone concentrations taught by Lohmann as this is an art-recognized concentration shown to produce an osteogenic effect on a roughened titanium surface. Moreover, generally, differences in ratios of excipients in a formulation will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such ratios are critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). Regarding the limitation of 1 µmol/l recited in instant Claim 61, this concentration falls between the higher (Cole) and lower (Lohmann) concentrations taught in the prior art. Accordingly, it would have been prima facie obvious to use an intermediate concentration as Applicants have not demonstrated any unexpected or unusual results, which accrue from a concentration of 1 µmol/l.

Claims 34 and 39 *remain* rejected under 35 U.S.C. 103(a) as being unpatentable over Steinemann *et al.* in WO00/44305; published: August 03, 2000, in view of Cole *et al.* in Clinical Orthopaedics and Related Research, 345, 219 – 228 (1997) as evidenced by Schrier *et al.* in AAPS PharmSciTech 2001; 2(3) article 18 and Israel et al. in US 2008/0139474 (published June 12, 2008), as applied to Claims 28 – 31, 33, 40, 42 – 60 and 63 – 70 above, and further in view of Brager *et al.* in Journal of Orthopaedic Research, 18, 133 – 139 (2000) as evidenced by Bab *et al.* in EMBO 11, 1867 – 1873 (1992).

Steinemann in combination with Cole teach an osteogenic implant, and preparation thereof, of a micro and macro roughened titanium surface and the transforming growth factor polypeptide (BMP-2) within the recited concentration and percent coating limitations.

The combination of Steinemann and Cole do not teach the limitation of instant Claims 34 and 39, in which the transforming growth factor polypeptide is osteogenic growth peptide.

Brager *et al.* teach the effect of administering exogenous osteogenic growth factor on fracture healing in the rat (page 138, discussion) as evidenced by increased mitogenicity and osteogenicity of marrow colonies in treated animals relative to controls (page 139, 2nd paragraph). The Brager reference, as noted above, teaches the osteogenic effect of the 14 amino acid polypeptide OGP (page 133, summary, 1st sentence) but does not disclose the sequence. As evidenced by, Bab *et al.*, the aforementioned 14 amino acid polypeptide is identical in sequence to that recited in instant Claim 39 (Bab, page 1868, Table 1).

It would have been *prima facie* obvious to one of ordinary skill in the art, at the time the invention was made, to cover the titanium implant of Steinemann with the known osteogenic polypeptide OGP. One would have been motivated to do so, with a reasonable expectation of success of providing an osteogenic implant, because administered OGP is known (Brager) to increase osteogenicity in fractures in the rat and other known transforming growth factor polypeptides such as bone morphogenic protein (BMP-2) when applied to a titanium implant (Cole) also provide an osteogenic effect.

Claim 32 *remains* rejected under 35 U.S.C. 103(a) as being unpatentable over Steinemann *et al.* in WO00/44305; published: August 03, 2000, Cole *et al.* in Clinical Orthopaedics and Related Research, 345, 219 – 228 (1997), as applied to Claims 28 – 31, 33, 40, 42 – 60 and 63 – 70 above, and further in view of Schmidmaier *et al.* in Bone, 28, 341 – 350 (2001).

Steinemann in combination with Cole teach an osteogenic implant, and preparation thereof, of a micro and macro roughened titanium surface and the transforming growth factor polypeptide (BMP-2) within the recited concentration and percent coating limitations.

The combination of Steinemann and Cole do not teach the limitation of instant Claim 32, in which the transforming growth factor polypeptide is selected from the transforming growth factors beta (TGF-β).

Schmidmaier *et al.* teach that local application of growth factors such as TGF-β1 on osteosynthetic implants accelerated fracture healing in rats (Title). Schmidmaier teaches that locally applied TGF-β1 accelerates fracture healing in a dose-dependent manner (page 341, Introduction, 2nd paragraph). Schmidmaier further teaches the effect on fracture healing in the rat with a titanium implant comprising TGF-β1 (page 343, Figure 1).

It would have been *prima facie* obvious for one of ordinary skill in the art, at the time of the invention, to cover the titanium surface of Steinemann with a transforming growth factor such as TGF-β1. One would have been motivated to do so with a reasonable expectation of successfully providing an osteogenic implant because

Schmidmaier teaches an accelerated healing effect on a bone fracture (an osteogenic effect) with a titanium implant coated with TGF-β1.

Claims 34 – 38 *remain* rejected under 35 U.S.C. 103(a) as being unpatentable over Steinemann *et al.* in WO00/44305; published: August 03, 2000, Cole *et al.* in Clinical Orthopaedics and Related Research, 345, 219 – 228 (1997) as applied to Claims 28 – 31, 33, 40, 42 – 60 and 63 – 70 above, and further in view of Kale *et al.* in US patent 6,811,776, filed: December 27, 2000 as evidenced by Bergmann in US patent 5,168,041).

Steinemann in combination with Cole teach an osteogenic implant, and preparation thereof, of a micro and macro roughened titanium surface and the transforming growth factor polypeptide (BMP-2) within the recited concentration and percent coating limitations.

The combination of Steinemann and Cole do not teach the limitation wherein the polypeptide is osteocalcin (instant Claim 34) or an osteocalcin having the formulas recited in instant Claims 35 – 38. It is noted that because the claims employ 'open language' the limitations are reasonably interpreted broadly as an osteocalcin comprising the recited sequences.

Kale teaches a method for *ex vivo* bone formation in the presence of osteogenic growth factors in addition to cDNA's encoding extracellular matrix proteins such as osteocalcin (column 4, lines 3 – 10). Kale further teaches that osteocalcin occupies 20% of the non-collagen protein of the bones and is presumed to have an important role in the formation of bone matrices (column 10, lines 66 – 67 and column 11, lines 1 – 9).

Kale teaches that human osteocalcin is a 49 amino acid protein but does not disclose the amino acid sequences for the osteocalcins recited in Claims 35 – 39. The sequences recited in Claims 35 – 39, as evidenced by Bergman, correspond to those found in human osteocalcin (Bergman, column 1, lines 24 – 30).

It would have been *prima facie* obvious to coat the titanium implant of Steinemann with the osteocalcin sequences corresponding to human osteocalcin. One would have been motivated to do so because Kale teaches that osteocalcin is a major component of protein in bones and has an important role in forming bone. Further, it would have been *prima facie* obvious to use amino acid sequences comprising human osteocalcin as a coating on the titanium implant of Steinemann with a reasonable expectation that the resulting composition would play a role in bone formation.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg,* 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman,* 11 F.3d 1046, 29 USPQ2d

2010 (Fed. Cir. 1993); *In re Longi,* 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Omum,* 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel,* 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 28 – 31, 33, 40 – 60 and 63 – 70 ***remain*** rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1 – 41 of Steinemann *et al.* in **US patent 6,702,855** in view of Cole *et al.* in Clinical Orthopaedics and Related Research, 345, 219 – 228 (1997).

Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons below:

The instant and copending Claims (Steinemann) are both drawn to surface modified (roughened) osteogenic titanium implants. Steinemann claims an implant comprising titanium having a roughened surface which is hydroxylated,, Steinemann claims an implant assembly comprising the titanium implant and a vessel at least

partially filled with water and inorganic salt additives. Steinemann claims a process for roughening the titanium surface by electrochemical or chemical etching. Steinemann does not claim covering the surface of the implant with a polypeptide. Cole teaches covering a titanium implant with the polypeptide BMP-2 and teaches said polypeptide-covered implants are osteogenic, i.e. enhance bone formation in rats.

It would have been *prima facie* obvious for one of ordinary skill in the art to cover the claimed titanium surface of Steinemann with the bone morphogenic protein, BMP-2, taught by Cole, to provide an osteogenic implant. One would have been motivated to do so, with a reasonable expectation of success, because Cole teaches that the combination of BMP-2 on a roughened titanium implant surface is osteogenic, i.e. enhances bone formation, in rats.

Response to Arguments

Applicant's arguments filed August 2, 2010 with respect to the maintained prior art 102(b) and 103(a) rejections cited above have been carefully considered but are not found to be persuasive.

With respect to the 102(b) rejection under Cole *et al.* as evidenced by Schrier *et al.* and Israel *et al.*, Applicant argues that "Cole teaches implants coated with BMP-2 and the ability of BMP-2 to remain osteoinductive and stimulate appositional bone formation. The coating process is described as simple even pipetting of a BMP-2 solution on the implants with subsequent drying in a laminar flow sterile hood. This process usually leads to an irregular protein deposit on the implant surface. Further, the

coated implants are implanted in a muscle pouch where they stimulate appositional bone formation. This is an artificial situation which may not be compared to the situation where the implant is positioned in a bone cavity" (Remarks, page 9, final paragraph).

Applicant argues that "Cole does not disclose monomolecular layer (monolayer) and in addition it does also not disclose how this coating is achieved, let alone how a partial monomolecular layer (monolayer) can be obtained" (Remarks, page 10, 1st paragraph).

These arguments are not found to be persuasive because, as noted in the Office Action mailed on February 2, 2010, Cole teaches bringing the same polypeptide (BMP-2) solution, into contact with a roughened titanium implant at the same concentrations recited in instant Claims 44 and 48. The active step of Cole is indistinct from the process embodiment recited in amended independent Claim 51 (applying to the metal surface of the implant a polypeptide). Accordingly, applying an amount of a hBMP-2 solution to the surface of the titanium implant will provide, absent evidence to the contrary, a monomolecular layer of peptide covering the same % of the surface recited in the instant Claims. Further, Applicant's argument that the contacting (applying) process of Cole leads to an irregular protein deposit on the implant surface is consistent with a rate of coverage of less than 100% as recited in the Claims (i.e. a portion of the implant is coated and a portion is not coated).

Finally, Applicant's argument directed to distinctions between the site of implantation (in a muscle pouch) and the subsequent effect (appositional bone formation) of the implant of Cole following implantation is not found to be persuasive

because one cannot show nonobviousness by attacking references individually (Cole) where the rejections are based on combinations of references (Steinemann in view of Cole). See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The Cole reference teaches the coating limitations and the motivation to apply the coating to the metal surface of the implant, while the primary reference, Steinemann, teaches introducing the implant into the cavity of a jaw bone.

Regarding the 103 rejections, in particular Steinemann in view of Cole, Applicant argues that "Steinemann WO 00/44305 discloses an implant consisting of titanium or a titanium alloy having a roughened, hydroxylated and hydrophilic surface. A method for producing and a method for storing such an implant are also described". Applicant argues that since neither Steinemann nor Cole (discussed above) teach a partial coating in the form of a monolayer, the same arguments as set forth in the response to the previous Office Action still apply" (Remarks, page 10, Section 103 and Double Patenting rejections, 1st – 3rd paragraphs). Applicant describes several features of the claimed implant, each of which is taught by Steinemann (as noted in the previous Office Action) and concludes that combining the teachings of Steinemann with the coatings of the cited references would achieve "an entirely different result". Applicant alleges that the cited references "tend to favor a maximized coating in terms of the amount of polypeptides and the surface covered. Thus, a skilled person is led in the opposite direction of the teachings of the present invention" (Remarks, page 11).

These arguments have been carefully considered but are not found to be persuasive because Steinemann, as noted in the maintained 103(a) rejection teaches all of the limitations for the titanium implant recited in the Claims absent the protein coating. Cole teaches contacting a hBMP-2 protein solution at the same concentration as claimed by Applicant. Accordingly, as noted on page 11 of the Office Action mailed February 2, 2010, it would have been obvious to combine the implant of Steinemann (indistinct from the titanium implant Claims) with the hBMP-2 coating of Cole by employing the same active step (contacting the implant with said solution) to provide the claimed coated implant (resulting in the recited % coverage and as a monolayer), in order to stimulate bone, absent evidence to the contrary.

Applicant's arguments that one of ordinary skill would have been motivated to maximize the amount of peptides and the surface covered is not found to be persuasive because the rejection is based solely on the teachings of the implant (Steinemann) and coating solution recited by Cole and not on whether a maximal coating was, in fact, desired or obtained by combining these references. The previously unappreciated properties of the resulting coated implant allegedly discovered by Applicant (a partially coated monolayer) would have been expected because the same elements (implant and protein solution) are combined using the same active step. Accordingly, although Cole is silent on the surface coverage and thickness of the protein coating, a partially coated monolayer would have resulted even if Cole had explicitly taught a *desire* to maximize the amount of peptides and the surface covered.

Applicant's argument that the Double Patenting rejection is rendered moot in view of the arguments provided in the Remarks filed August 2, 2010 (Remarks, page 12) is not found to be persuasive because, as noted above, Applicant's arguments regarding the maintained 103 rejection (Steinemann in view of Cole) have not been found to be persuasive.

Conclusion

Claims 28 – 70 are rejected. No claims are allowed.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DENNIS HEYER whose telephone number is (571)270-7677. The examiner can normally be reached on Monday-Thursday 8AM-5PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, BRANDON FETTEROLF can be reached at (571)272-2919. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

DH

/Brandon J Fetterolf/

Supervisory Patent Examiner, Art Unit 1628